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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,766	05/10/2006	Thomas A. Beyer	PC25123A	6301

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PFIZER INC.
PATENT DEPARTMENT, MS8260-1611
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EXAMINER	
JAISLE, CECILIA M	

ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
02/06/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

~IPGSGro@pfizer.com

Office Action Summary	Application No.	Applicant(s)	
	10/595,766	BEYER ET AL.	
	Examiner	Art Unit	
	CECILIA M. JAISLE	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,12-14,16-18,20 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-5,16,17 and 21* is/are allowed.

6)☒ Claim(s) *6-8,12-14,18 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-17-2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Lack of Unity

Applicants' election of Group I without traverse in the Response of Dec. 13, 2007 is acknowledged. Claims 1-8, 12-14, 16-18, 20 and 21, all claims in this application, drawn to pyrido[2,3-d]pyrimidine compounds, pharmaceutical compositions comprising them and pharmaceutical methods using them, are under examination on their merits.

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-8, 12-14, 18 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of bone fracture and promotion of bone in-growth in rats with the compounds of Examples 1-37, does not reasonably provide enablement for a method of treating all PDE2-mediated conditions, diseases or symptoms with all of the millions of compounds and compositions construed by the claims for treating osteoporosis, pulmonary hypertension, female sexual arousal disorder, diminished memory or cognition, platelet aggregation, vascular angiogenesis, dementia, cancer, arrhythmia, thrombosis, bone fracture and/or defect, delayed or non-union fracture, spinal fusion, bone in-growth, cranial facial reconstruction, or hypoxia in mammals, broadly. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) the claim breadth; (2) the nature of the invention; (3) the state of the prior art; (4) the level of predictability in the art; (5) the amount of direction provided by the inventor; (6) the presence of working examples; and (7) the quantity of experimentation needed to use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for hepatitis B surface antigen detection did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (Fed.Cir. 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement:

1. **Breadth of the claims:**

(a) Scope of the compounds. The claims cover potentially millions of compounds of Formula (I). When EP2 selective receptor agonists are added, the potential compositions grow to the billions.

(b) Scope of the diseases covered. Claims 6 and 18 are directed to a method for treating PDE2 mediated condition, disease or symptom in a mammal. The claimed scope includes the recited disorders of the other method claims as well as

undiscovered disorders/conditions associated with PDE2 for which there is no enabling disclosure. The full scope of claim 6 is unknown.

Claims 7 and 8 are directed to methods for treating osteoporosis, pulmonary hypertension, female sexual arousal disorder, diminished memory or cognition, platelet aggregation, vascular angiogenesis, dementia, cancer, arrhythmia, thrombosis, bone fracture and/or defect, delayed or non-union fracture, spinal fusion, bone in-growth, cranial facial reconstruction, or hypoxia in mammals, broadly.

Claims 12-14 and 20 are directed a method of claims 6-8 with the addition of a therapeutically effective amount of an EP2 selective receptor agonist.

Primary or unexplained pulmonary hypertension (PPH) is a rare lung disorder in which blood pressure in the pulmonary artery rises far above normal levels for no apparent reason. PPH patients respond differently to different medications that dilate blood vessels and no one drug is consistently effective in all patients. Because individual reactions vary, different drugs have to be tried before chronic or long-term treatment begins. During the course of the disease, the amount and type of medicine also may have to be changed. At present, about one-quarter of patients can be treated with calcium channel-blocking drugs given orally. Intravenous prostacyclin helps patients nonresponsive to calcium channel blockers. Clinical trials are under way to evaluate anticoagulants and diuretics. A good animal model of PPH is still unavailable.

Female sexual arousal disorder (FSD) is a condition of decreased, insufficient or absent lubrication in females during sex. Because the relationship between the woman and her partner plays a significant role in development and maintenance of sexual problems, most programs are designed to be implemented by the couple, although additional strategies may focus on the individual. Animal models are unavailable. Pharmaceutical companies are beginning to promote products to treat FSD, often involving low doses of testosterone.

Diminished memory or cognition has been linked generally with such diverse conditions as reduced B12 and folate, Huntington's Disease, narcolepsy, migraines, fetal alcohol syndrome, and many other conditions.

Angiogenesis, formation of new blood vessels from pre-existing vascular structures, is both a necessary developmental and survival process with potential to also be detrimental, promoting certain disease processes. During wound healing, embryonic development and menses, angiogenesis provides developing tissues with necessary nutrients and oxygenation. Indeed, stimulating angiogenesis after injury has been proposed as a means of reducing damage that often accompanies reperfusion of ischemic tissues after injury. In contrast, aberrant or excessive angiogenesis allows vascularization of solid tumors and provides routes through which cancer cells may metastasize. A better understanding of steps controlling angiogenesis should further advance attempts to stimulate angiogenesis when warranted and inhibit it when required. Inhibition of angiogenesis would clearly be beneficial in limiting growth of solid tumors, progression of diabetic retinopathy and

chronic inflammation associated with rheumatoid arthritis. Stimulating angiogenesis could have beneficial consequences in treatment of coronary artery disease and in limb ischemia associated with diabetes.

Angiogenesis requires cooperation of several distinct cell types; vascular endothelial cells (VECs) are perhaps most important. VECs line every blood vessel and constitute the majority of capillary cells. VECs' ability to emerge from their basement membrane and migrate toward an angiogenic stimulus is thought to initiate the neovascularization process. Tumors, activated lymphocytes or wound-associated macrophages can release such proangiogenesis stimuli. Vascular endothelial growth factor (VEGF) is probably the most widely acknowledged angiogenesis initiator. VEGF released from tumor cells, macrophages and other immune cells in response to hypoxia stimulates vascular relaxation (a prerequisite for endothelial cells to enter the angiogenic cascade) *via* NO production by VECs, increases VEC permeability and increases VEC VEGF receptor expression during hypoxia or ischemia. In addition, other potent positive angiogenesis regulators are basic fibroblast growth factor (bFGF), acidic fibroblast growth factor and transforming growth factor.

Cancer includes such diverse diseases as breast cancer, adenocarcinoma of the esophagus and gastroesophageal junction, hepatocellular carcinoma, cervical carcinoma, colorectal cancer, human prostate cancer, and lung tumor, none of which are enabled and many of which are currently considered fatal.

Hepatocellular carcinoma (HCC) is a primary malignancy of the hepatocyte, generally leading to death. HCC frequently arises in relation to cirrhosis. The extent

of hepatic dysfunction limits treatment options, and as many patients die of liver failure as from tumor progression. Available treatment options depend on the size, number, and location of tumors; presence or absence of cirrhosis; operative risk based on extent of cirrhosis and comorbid diseases; overall performance status; patency of portal vein; and presence of metastatic disease. Surgical resection and liver transplantation offer the only chances of cure.

Breast cancers are of great variety. The most important category of breast cancers is ductal cancers, which are of a wide variety of types. Presently, they are divided into these categories: Intraductal (in situ); Invasive with predominant intraductal component; Invasive, NOS; Comedo; Inflammatory (IBC); Medullary with lymphocytic infiltrate; Mucinous Carcinoma (colloid carcinoma); Papillary carcinoma; Scirrhous; Tubular and Other. Another category is Lobular breast cancers, which can be in situ, Invasive with predominant in situ component and Invasive. Paget's disease of the nipple can be also have intraductal carcinoma or invasive ductal carcinoma. Adenomyoepithelioma is a dimorphic tumor characterized by presence of both epithelial and myoepithelial cells. There is breast angiolipoma, spindle cell lipoma of the breast and lymphoma of the breast (both Non-Hodgkin's lymphoma of the breast and Hodgkin's disease of breast forms). Some sarcomas of the breast include giant cell sarcoma, leiomyosarcoma, Angiosarcoma, cystosarcoma phylloides and liposarcoma. Carcinoid tumors can be primary carcinoid tumors of the breast or can arise from nonmammary sources. Breast salivary gland-like tumors include acinic cell carcinoma (AcCC), oncocytic carcinoma (Mammary

epithelial oncocytoma) and mucoepidermoid carcinoma (MEC). Other rare carcinomas of the breast include Spindle cell carcinoma (SpCC), Squamous cell carcinoma, Secretory Carcinoma (Juvenile secretory carcinoma), Metaplastic carcinoma (a heterogeneous group of invasive cancers including types with squamous differentiation and heterologous elements), Invasive Micropapillary Carcinoma, Adenoid cystic carcinoma, cribriform carcinoma, Myofibroblastoma (Benign spindle stromal tumor) and glycogen-rich clear cell carcinoma. Numerous other rare breast cancers include for example Fibromatosis (extra-abdominal desmoid), Angiomatosis and mammary hamartoma. Nonmammary tumors, primarily adenocarcinomas, can metastasize to the breast, including bronchogenic carcinomas, malignant melanomas (primary and secondary), rhabdomyosarcomas, malignant mesotheliomas, thyroid carcinomas, renal cell carcinomas, malignant lymphomas and gastrointestinal carcinomas (including those from the stomach, pancreas, esophagus and colon).

Adenocarcinoma of the esophagus or gastroesophageal junction (GEJ) is an aggressive disease with early lymphatic and hematogenous dissemination. Molecular pathology has revealed many molecular mechanisms of disease progression. Adenocarcinomas of the esophagus and GEJ show multiple genetic alterations, which indicate that progression of cancer is a multistep complex process with many different alterations. Presumably, it is not one molecular factor that can predict the biological behavior of this cancer.

Colorectal cancers include many diverse types. Most are adenocarcinomas, either of the mucinous (colloid) type or the signet ring type. Less common colorectal cancers include squamous cell, neuroendocrine carcinomas, carcinomas of scirrhous type, lymphomas, melanomas (primary or metastatic), sarcomas (including fibrosarcomas and Leiomyosarcomas) and Carcinoid tumors.

Prostate carcinomas include adenocarcinomas; small cell, mucinous, basal cell, neuro-endocrine, signet-ring cell and prostatic ductal carcinomas; squamous cell carcinoma of the prostate; and others.

Thrombosis and thrombotic disorders include such diverse conditions as venous thromboembolism, Portal vein thrombosis, Renal vein thrombosis, hepatic vein thrombosis (Budd-Chiari syndrome), Paget-Schroetter disease (upper extremity vein), Thoracic outlet syndrome, Subclavian Vein Thrombosis, Arterial thrombosis, Stroke (thrombotic or embolic), Myocardial infarction, Thoracic outlet syndrome, Embolisation, pyemia, septic embolus, Hypertensive heart disease, Hypertensive nephropathy, Secondary hypertension, Renovascular hypertension, Angina pectoris, Prinzmetal's angina, Myocardial infarction, Dressler's syndrome, Pulmonary embolism, Cor pulmonale, Pericarditis, Cardiac tamponade, Endocarditis, Mitral regurgitation, Mitral valve prolapse, Mitral stenosis, Aortic valve stenosis, Aortic insufficiency, Pulmonary valve stenosis, Myocarditis - Cardiomyopathy (Dilated cardiomyopathy, Hypertrophic cardiomyopathy, Restrictive cardiomyopathy), Arrhythmogenic right ventricular dysplasia, *AV block* (First degree, Second degree, Third degree), Bundle branch block (Left, Right), Bifascicular block, Trifascicular

block, Wolff-Parkinson-White syndrome, Lown-Ganong-Levine syndrome, Long QT syndrome, Cardiac arrest, Arrhythmia: Paroxysmal tachycardia (Supraventricular, AV nodal reentrant, Ventricular), Atrial flutter, Atrial fibrillation, Ventricular fibrillation, *Premature contraction* (Atrial, Ventricular), Sick sinus syndrome, Heart failure, Cardiomegaly, Ventricular hypertrophy (Left, Right), Atherosclerosis (Renal artery stenosis), Aortic dissection, Raynaud's phenomenon/Raynaud's disease, Buerger's disease, Intermittent claudication, Hereditary hemorrhagic telangiectasia, Spider angioma, Thrombosis/Phlebitis/Thrombophlebitis (Deep vein thrombosis, May-Thurner syndrome, Portal vein thrombosis, Venous thrombosis, Budd-Chiari syndrome, Renal vein thrombosis, Paget-Schroetter disease), Varicose veins (Hemorrhoid, Esophageal varices, Varicocele, Gastric varices, Caput medusae), Superior vena cava syndrome, *Lymph*(Lymphadenopathy, Lymphedema), and congenital thrombotic disorders including Ventricular septal defect, Atrial septal defect (Lutembacher's syndrome), Atrioventricular septal defect, Tetralogy of Fallot, Eisenmenger's syndrome, Pulmonary valve stenosis, Tricuspid atresia, Ebstein's anomaly, Aortic valve stenosis, Aortic insufficiency, Bicuspid aortic valve, Mitral stenosis, Mitral regurgitation, Hypoplastic left heart syndrome, Dextrocardia, Levocardia, Cor triatriatum, Patent ductus arteriosus, Aortic coarctation, Overriding aorta, Aneurysm of sinus of Valsalva, Pulmonary atresia, Persistent left superior vena cava, Total anomalous pulmonary venous connection, Scimitar syndrome, Arteriovenous malformation (Cerebral arteriovenous malformation).

The specification fails to identify the results of treatment with the compounds of this invention and how such results would be recognized, particularly with regard to cancers and other conditions and diseases that are currently considered fatal.

2. **Nature of the invention and predictability in the art:** The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present:

> The first paragraph of 35 U.S.C. §112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

Plant Genetic Systems N.V. v. DeKalb Genetics Corp., 65 USPQ2d 1452, 1456 (Fed.Cir. 2003).

3. **Direction and Guidance:** That provided is very limited. The dosage range information is meager at best. It is generic, the same for all disorders the specification covers. No specific direction or guidance provides a regimen or dosage effective specifically for all of the conditions construed by the claims.
4. **State of the prior art:** These compounds are amino pyrido[2,3-d]pyrimidines with a particular substitution pattern. No amino pyrido[2,3-d]pyrimidines of any kind have been used for treatment of the diseases here described. See the detailed discussions below of Bonnet, European Urology, Murray, Wharton, Rutten, Boess,

Mseeh, Kishi, Favor, Fiscus, Shimizu, Murata, Fryknas, Dy, Herring, Galindo-Tover, Favot, Sim, and Phillips.

5. **Working Examples:** The examples only show treatment of bone fracture and promotion of bone in-growth in rats with the compounds of Examples 1-37. Applicants do not provide highly predictive competent evidence or recognized tests to treat all conditions recited for the claimed compounds.

Applicants provide no competent evidence that all of the compounds of Formula I, alone or in combination with all EP2 selective receptor agonists, will effectively treat all of the diseases, conditions and symptoms construed by the claims. Furthermore, Applicants have not provided competent evidence that the instantly disclosed tests are highly predictive for all uses disclosed and embraced by the claim language for all of the intended hosts.

6. **Skill of those in the art:** With regard to osteoporosis, bone fracture and/or defect, delayed or non-union fracture, spinal fusion, bone in-growth, cranial facial reconstruction, Bonnet, et al., Toxicology and Applied Pharmacology, 221 (2007), 111-118, report that "serious issues have been raised regarding the potential use of PDE inhibitor for bone treatment. … [T]he complexity of PDE inhibitors action on bone cells and the lack of *in vivo* data require further study." Bonnet further suggests combinations of different PDE inhibitors ("…a combination of PDE4 and PDE2 inhibitors is more efficient that a specific PDE4 inhibitor"), and the report concludes, "However, clinical trials as well as further basic studies will be needed to substantiate the efficacy of PDE inhibitors…" Regarding any relationship between

PDE2 inhibition and osteoporosis, Bonnet, at p. 115, "… noted a higher beneficial effect of tofisopam compared to rolipram, suggesting a role of PDE4 but also of PDE2 in the bone metabolism."

Regarding a relationship between PDE2 inhibition and female sexual arousal disorder, European Urology, UroToday, Vol. 50, No. 6, pp. 1194-1207 (Dec. 2007), studied various PDE isoenzymes in their effects female sexual dysfunction and, although they noted, p. 1204, " … immunosignals related to PDE2, 4 and 4A were shown in subepithelial blood vessels; the fibromuscular stroma, sinusoidal endothelial and subendothelial layers; and in nerve fibers, respectively, of the clitoris …", concluded, p. 1204, "Taken together, morphologic and preclinical findings are in favor of a role for PDE5 in the regulation of female genital vascular responses."

With regard to pulmonary hypertension, Murray, et al., Am. J. Physiol. Lung Cell. & Mol. Physiol. 292, L294-L303, 2007, reports:

> Consistent with the patterns observed for increased expression of the PDE isoforms …, PDE1 and PDE3 inhibitors were more effective than PDE2 and PDE4 inhibitors in enhancing cAMP in response to forskolin in IPAH [idiopathic pulmonary arterial hypertension] and SPH PASMC [secondary pulmonary hypertension, pulmonary arterial smooth muscle cells] compared with controls.

Regarding a relationship between PDE2 inhibition and pulmonary hypertension, Wharton, et al., Am. J. of Respiratory and Critical Care Medicine, Vol. 172, 2005, pp. 105-113, compared PDE2, PDE5 and other PDE isoforms in their effects on human pulmonary artery cell growth and recommended that, not PDE2, but PDE5 "… inhibition represents a novel strategy for the treatment of pulmonary hypertension."

Regarding memory or cognition, Rutten, et al., Eur. J. of Pharmacol. 558 (2007), 107-112, observed, "Post-hoc analysis revealed that the *d*2 values [index of object discrimination] were higher than those of the vehicle condition, when the rats were injected with the PDE201 directly after, or 3 h after trial 1, but not when injected 1 h or 6 h after trial 1." It is also to be noted that these were normal rats, not rats that had been determined to be of *diminished* memory or cognition.

Regarding any relationship between PDE2 inhibition and diminished memory and cognition, Boess, et al., Neuropharmacology 47 (2004), pp. 1081-1092, cautiously suggested "Increasing or restoring normal neuronal cGMP levels with the help of PDE2 inhibitors may, therefore, represent a novel therapeutic approach to improve memory performance in conditions in which the NO/cGMP signal transduction pathway is impaired, such as in Alzheimer's disease and other memory disorders."

Regarding platelet aggregation, Mseeh, et al., Thromb. Res., 98 (2000), 395-401, recognized, "Little is known about the catalytic site of PDE2," and expressed the hope, "PDE2 inhibitors could eventually be developed as anti-platelet drugs that could be used separately or together with inhibitory prostaglandins at low doses."

Regarding any relationship between PDE2 inhibition and platelet aggregation, Kishi, et al., Cardiovascular Drug Reviews, Vol. 19, No. 3, 2001, pp. 215-225, studied ibudilast, a nonselective PDE and platelet aggregation inhibitor, and cautiously suggested:

> …ibudilast is a strong inhibitor of PDE2 and 4, which are major isozymes of endothelial cells. Since endothelial function is extremely important for the maintenance of vascular integrity and since its dysfunction leads to atherosclerosis and vascular

> remodeling, the action of ibudilast on endothelial metabolism should be further investigated.

With regard to vascular angiogenesis, Favor, et al., Thromb. Haemost. 2003 Aug;90(2):334-43 (PubMed abstract), report the need for further research, "These data strongly suggest that PDE2 and PDE4 represent new potential therapeutic targets in pathological angiogenesis."

Similarly regarding dementia, Fiscus, Neurosignals 2002:11:175-190, report the need for further research, "Further studies will be needed to elucidate the role of PDE2 and PDE3 as downstream targets of cGMP in neural cells and the potential involvement in cGMP-mediated neuroprotection."

Cancer covers a wide variety of diseases of different causes and therapy.

Murata, et al., Clin. & Experim. Metastasis, 18:599-604 (2001), cautiously report, "…there is a PDE4 activity dominant in DLD-1 cells [a **colon cancer cell line**], and that PDE2 and PDE3 activities against cAMP were very low if any. … This indicated that cGMP levels are not high enough to activate PDE2 in intact DLD-1 cells…"

Regarding any relationship between PDE2 inhibition and cancer, Fryknas, et al., Molecular Screening for Target Discovery in Cancer, 2006, 44 pages, Paper No. III, cautiously noted, and only in regard to **human squamous cell carcinoma**, p. 28, "Combination of annotated compound libraries and expressional profiling seems to be an approach effective for target identification, here suggesting PDE2 and PDE3 as potential drugs for treatment of squamous cell carcinomas." Dy, et al., J. Clin. Oncol., Vol. 20, No. 13 (Jul. 2002) pp. 3016-3028, in regard to only **human colon tumor cell lines**, acknowledged, P. 3019, "In human colon tumor cell lines,

apoptosis is induced as exisulind-inhibited cGMP PDE of either the PDE2 or PDE5 isozyme families, thereby causing a sustained increase in cGMP and the activation of cGMP-dependent protein kinase G."

Regarding arrhythmia, Herring, et al., J. Physiol. (2001), 535.2, pp. 507-518, concluded, "…inhibition of PDE 2 has no effect on the HR [heart rate] response to vagal nerve stimulation …" and "Inhibition of PKA also abolished the augmentation of vagal bradycardia by SNP whilst inhibition of PDE 2 or PKG had no effect."

Regarding any relationship between PDE2 inhibition and arrhythmia, Galindo-Tover, et al., Brit. J. Pharmacol. (2007), 1-11, noted in testing of various PDE isoforms, p. 9, "Our results with ventricular arrhythmias are consistent with results in isolated cardiomycetes from adult mice in which the PDE4D3 isoform was found to participate in a macromolecular complex including RyR2 and PKA …", while regarding the role of PDE2, they noted "A possible reason for the lack of $ß_2$-adrenoceptor-mediated responses in right ventricle could be an involvement of PDE2, an option which requires further research."

Favot, et al., Bereich NIMMT, Vol. 90, Aug. 2003, pp. 334-343 (abst.), regarding thrombosis, recommend further research, "These data strongly suggest that PDE2 and PDE4 represent new potential therapeutic targets in pathological angiogenesis."

Regarding a relationship between PDE2 inhibition and thrombosis, Sim, et al., Blood, 03-2004, Vol. 103, No. 6, 2127-2134, recognized, p. 2132, "Clinical studies have shown that PDE3A inhibitors are effective in preventing arterial thrombosis."

Regarding any relationship between PDE2 inhibition and bone fracture, bone defect, Bonnet, p. 117, suggested that PDE4, PDE3 and PDE2 inhibitors "are potential new candidates for osteoporosis treatment," recognized some limitations of their study:

> First we have not compared the antidepressant treatments with classic anti-osteoporotic treatment … to know if some antidepressants can also protect from bone deterioration as well as anti-osteoporotic treatments. Secondly histomorphometric data would be useful to better understand the effect on bone remodeling, and confirm the bone markers data.

and concluded, "… caution should be taken until further fundamental and clinical data exist."

With regard to hypoxia and pulmonary hypertension, Phillips, et al., Am. J. Physiol. Lung Cell Mol. Physiol. 288, L103-L115, 2005, described the focus of their study:

> …we established the effects of isoform-selective PDE inhibitors and the prostacyclin analog cicaprost on acute hypoxia-induced pulmonary vasoconstriction using an in situ perfused rat lung preparation, and we determined the effect of the prostacyclin analog iloprost alone and in combination with PFE inhibitors on the hemodynamic and structural changes of pulmonary hypertension in the chronically hypoxic rat model,

disappointingly report, "…PDE2 activity in rat pulmonary arteries is low or negligible (as is the case in humans) and/or does not significantly contribute to cyclic nucleotide metabolism in PASMC [pulmonary artery smooth muscle cells]."

and concluded:

> our data suggest that the combination of subtherapeutic concentrations of existing therapies (e.g., prostacyclin or iloprost) with these agents [individual PDE isoform inhibitors], or indeed the

> combination of individual PDE isoform inhibitors (e.g., PDE3 and PDE4), may lead to a therapeutic effect on acute and chronic pulmonary vascular response to hypoxia without significant systemic hypotension.

Note that the Phillips study failed to establish any relationship between PDE2 inhibition and hypoxia.

7. **Quantity of experimentation needed to make or use the invention.** Based on the disclosure's content, an undue burden would be placed on one skilled in the pharmaceutical arts to make and use the invention, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for reasons explained above. The state of the art, as discussed in the articles referenced above, indicates the requirement for undue experimentation. Thus, the ability of an agent that inhibits PDE-2 to ameliorate all of the diseases/conditions/symptoms recited by the present claims remains open to further study and proof.

Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. See *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). Also, note *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding types of testing needed to support *in vivo* uses. Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099 (2001), emphasizing that "a claimed invention must have a specific and substantial utility." See also MPEP 2163, *et. seq*. The disclosure in this application is not sufficient to enable the instantly claimed methods based solely on disclosure of inhibition of PDE-4 by compounds of Formula (I).

MPEP 2164.01(a) states,

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above [Wand] factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed.Cir. 1993).

The above consideration clearly justifies that conclusion here and undue experimentation would be required to practice Applicants' invention. The consideration of the above factors demonstrates that the present application does not sufficiently enable the present claims. In view of the pharmaceutical nature of the invention, the unpredictability of relationship between PDE-2 and specific diseases/conditions, one of ordinary skill in this art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Allowed Claims

Claims 1-5, 16, 17 and 21 are allowed. Jonas, et al., WO/2002/00660, published Jan. 3, 2002 (cited by Applicants), describes 5-aminoalkyl-pyrazolo[4,3-d]pyrimidines with a phosphodiesterase V-inhibiting effect. However, the presently claimed compounds distinguish patentably from all of the compounds therein disclosed, as well as over all other prior art of record herein.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CECILIA M. JAISLE, J.D. whose telephone number is (571)272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James O. Wilson/
Supervisory Patent Examiner
Art Unit 1624

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